# DISSOLUTION AND DISSOLUTION TESTING

**James L. Ford**
*Liverpool John Moores University, Liverpool, United Kingdom*

**Ali R. Rajabi-Siahboomi**
*Colorcon Limited, Kent, United Kingdom*

## INTRODUCTION

Dissolution tests are one of the tests most used in the characterization of drugs and in the quality control of dosage forms. During the late 1960s it became recognised that dissolution data should be determined by studying the rate at which dosage forms allow their formulated drug to dissolve. Subsequently, dissolution tests for six products were introduced into the USP 18 (1969). This increased to about 600 tests in the USP 24, which also includes drug-release requirements for modified release products and transdermals.

Although dissolution tests are mainly used as quality control methods to ensure end-product or batch-to-batch consistency and to identify good and bad formulations, dissolution data may also be correlated with in vivo activity. Dissolution tests become especially important if dissolution is the rate-limiting step in drug absorption. Dissolution tests are, therefore, used to confirm compliance with compendial specifications and are needed as part of a product licence application. Additionally they are used during product development and stability testing as part of the specification for the product. No universal dissolution test has been designed that gives the same rank order for in vitro dissolution and in vivo bioavailability from different formulations and batches.

## MATHEMATICAL CONCEPTS OF DISSOLUTION

### Dissolution of Particles

Eq. 1 is one of the oldest expressions used to describe the dissolution process of a particle:

$$\frac{dW}{dt} = \frac{D}{h} S(C_s - C_t) \tag{1}$$

where $dW/dt$ is the rate at which a material dissolves across a surface $S$ at a time $t$; $C_s - C_t$ is the concentration gradient between the concentration of solute in the stagnant layer (thickness $h$ and immediately adjacent to the dissolving surface) surrounding the dissolving particles, and is assumed to be equal to the difference between the saturated solubility of the drug ($C_s$) and the concentration of the solute in the surrounding medium at time $t$ ($C_t$). The parameter $D$ is a function of the diffusion coefficient of the solute molecules. Maximum dissolution rates are predicted when $C_t = 0$. Consequently, as $C_t$ increases, the dissolution rate decreases. The parameter $D$ is also dependent on $C_s - C_t$. Such conditions, where dissolution is followed by absorption of the drug, an in vivo situation, are described as sink conditions (i.e., $C_t < 0.1\ C_s$). In vitro systems should ideally maintain a sink condition and the dissolving solid should be tested in fresh solvent.

In Eq. 1 the parameter $D$ is temperature dependent. Consequently, both the temperature of the dissolution fluid and its viscosity (which is also temperature dependent) should be carefully controlled. In addition, the presence of electrolytes and changes in pH may influence the diffusing species by altering their ionization. Such factors imply that dissolution fluids should be as simple as possible.

The constraints imposed by sink conditions may be overcome using various approaches. It may be accepted that non-sink conditions apply and that incomplete dissolution will occur. Alternatively, corrections may be made by increasing the volume of the dissolution fluids, removal of the dissolved drug by partition from the aqueous phase of the dissolution fluid to an organic phase either above or below the dissolution fluid, addition of selective adsorbents to remove the dissolved drug, addition of a water-miscible solvent to the dissolution media to increase drug solubility or removal of dissolved drug, using a flow-through system.

### Dissolution of a Mono-Dispersed Powder

Dissolution processes of multiparticulate systems where the specific surface area decrease during the dissolution,

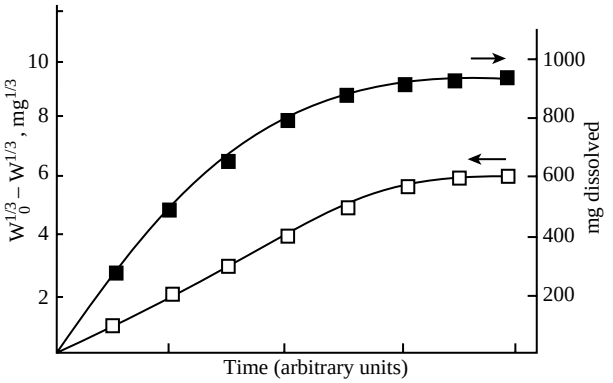


**Fig. 1** Dissolution data for a hypothetical solid plotted as cumulative amount released (right axis) and after cube-root-law data treatment (left axis).

may be described by the Hixson and Crowell (1) cube root law in Eq. 2:

$$W_0^{1/3} - W^{1/3} = Kt \tag{2}$$

where $W_0$ represents the original mass of drug, $W$ is the amount of remaining drug at time $t$, and $K$ is the dissolution rate constant. Fig. 1 represents a typical plot where a straight-line release exists throughout the substantial period of the dissolution. The cube-root law assumes several factors, including a constant diffusion layer thickness, isotropicity of the sample, an independence of solubility of particle size, smooth surfaces, and sink conditions. Modifications of the equation are required for non-sink conditions and polydisperse systems; for example, Lai and Carstensen (2) derived shape factors to modify cube root behavior. In reality, dissolution from multiparticulate systems requires more complex mathematical approaches to dissolution. Associated problems include correctly assigning the particle size distribution to the powders, the fact that small particles have higher solubilities than larger ones, and accounting for changes in both the size and the number of particles during dissolution.

### Dissolution of Disintegrating Tablets and Capsules

The development of theories of dissolution from disintegrating tablets and capsules becomes very difficult because disintegration produces vast changes in surface area. Attempts have been made to develop models to describe dissolution rates from tablets, using complex mathematical approaches (3, 4).

### Dissolution of Nondisintegrating Tablets

For systems where drug release involves the dissolution of a soluble drug at high concentrations from an insoluble matrix, the Higuchi (5) equation adequately describes release rates (Eq. 3):

$$\frac{W_r}{t^{1/2}} = 2W_0\frac{S}{V}(D/\pi\tau)^{1/2} \tag{3}$$

where $W_r$ is the amount of drug dissolved in time $t$; $W_0$ is the dose of the drug; $S$ is the effective diffusional area; $V$ is the volume of the hydrated matrix; $D$ is the diffusion coefficient of the drug in the hydrated matrix; and $\tau$ is the tortuosity of the matrix. An analogous equation was developed for drugs of limited water solubility (6).

It is not the aim of this article to evaluate formulation aspects that may influence dissolution of drugs from dosage forms. However, it suffices to mention that dissolution rates from unformulated powders or tablets may be increased or decreased according to many factors, including salt selection, the presence of surfactants, polymorphic modifications, and the use of water-soluble carriers as in solid dispersions.

Having identified some of the important criteria and models for dissolution, let us examine some of the apparatus used to measure dissolution rates.

## DESIGN OF APPARATUS

The ideal features of a dissolution apparatus are (7):

1. The fabrication, dimensions, and positioning of all components must be precisely specified and reproducible, run to run.
2. The apparatus must be simply designed, easy to operate, and useable under a variety of conditions.
3. The apparatus must be sensitive enough to reveal process changes and formulation differences but still yield repeatable results under identical conditions.
4. The apparatus, in most cases, should permit controlled variable intensity of mild, uniform, nonturbulent liquid agitation. Uniform flow is essential because changes in hydrodynamic flow will modify dissolution.
5. Nearly perfect sink conditions should be maintained.
6. The apparatus should provide an easy means of introducing the dosage form into the dissolution medium and holding it, once immersed, in a regular reliable fashion.
7. The apparatus should provide minimum mechanical abrasion to the dosage form (with exceptions) during

the test period to avoid disruption of the microenvironment surrounding the dissolving form.

8. Evaporation of the solvent medium must be eliminated, and the medium must be maintained at a fixed temperature within a specified narrow range. Most apparatuses are thermostatically controlled at around 37°C.
9. Samples should be easily withdrawn for automatic or manual analysis without interrupting the flow characteristics of the liquid. In the latter case, efficient filtering should be achieved.
10. The apparatus should be capable of allowing the evaluation of disintegrating, nondisintegrating, dense or floating tablets or capsules, and finely powdered drugs.
11. The apparatus should allow good interlaboratory agreement.

There are two principal types of apparatus design. One is based on limited volume that is constrained to the size of the container used. The second type uses a continuous-flow cell to house the dosage form and permits constant replenishment of the dissolution fluids.

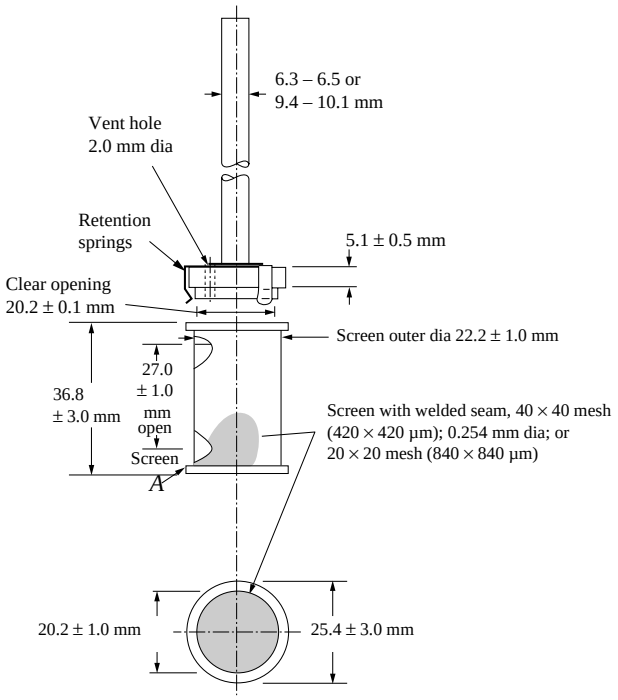


**Fig. 2** The basket stirring element of the United States Pharmacopeia 24. (From Ref. 8.)

## COMPENDIAL APPARATUS WITH FIXED VOLUMES OF DISSOLUTION FLUID

The general principle of dissolution tests is that the powder or solid dosage form is tested under uniform agitation, which is accomplished by either using a stirrer inside the apparatus or rotating the container holding the dosage form (e.g., a basket). Two general methods are currently included in the USP 24 (8) and the BP 2000 (9) to measure dissolution from tablets and capsules. In apparatus 1, the dosage forms are enclosed in a basket; in apparatus 2, agitation is provided by means of a paddle. Each apparatus is a limited volume-type apparatus.

### Basket Apparatus

The basket method was first described in 1968 by Pernarowski et al. (10). A container, the basket, constrained the enclosed tablet or capsule, allowed for fluid change and could be used either in continuous flow or in restricted volume modes. This gradually evolved to the USP 24 (8) and BP 2000 (9) apparatus 1—the rotating basket apparatus (Fig. 2). The dimensions are taken from the USP 24, although those given in the BP 2000 are similar. The apparatus consists of a motor, a metallic drive shaft, a cylindrical basket, and a covered vessel made of glass or other inert transparent material. The latter should be made of materials that do not sorb or react with the specimen being tested. The contents are held at 37 ± 0.5°C. There should be no significant motion, agitation, or vibration caused by anything other than the smoothly rotating stirring element. Ideally, the apparatus should provide observation of the stirring element and specimen. The vessel is cylindrical with a hemispherical bottom and sides that are flanged at the top. It is 160–210 mm high and has an inside diameter of 98–106 mm, and a nominal capacity of 1000 ml. Other sizes are described for 2 and 4 L capacity vessels. A fitted cover may be used to retard evaporation but should provide sufficient openings to allow ready insertion of a thermometer and allow withdrawal of samples for analysis. The shaft is so positioned that its axis is no more than 2 mm at any point from the vertical axis of the vessel and should rotate smoothly, without significant wobble. The shaft rotation speed should be maintained within ±4% of the rate specified in the individual monograph. The shaft has a vent and three spring clips or other suitable means to fit the basket into position. Each should be fabricated of stainless steel, type 316 or equivalent. Welded seam, stainless steel cloth (40 mesh or 425 μm) is used, unless an alternative is specified. For testing, a dosage unit is placed in a dry basket at the beginning of each test. The distance

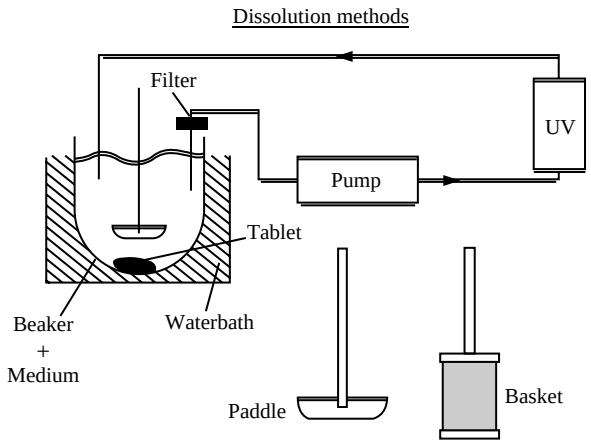


**Fig. 3** Typical apparatus set up for basket and paddle apparatus.

between the inside bottom of the vessel and the basket is 25 ± 2 mm. Typical arrangements for the apparatus are shown in Fig. 3.

Although the basket apparatus in the BP 2000 and USP 24 are similar and have a common design, considerable changes have taken place since basket apparatuses were first included in official monographs. The USP 18 (11) described a cylindrical vessel with a slightly concave bottom. No precise specifications were given for the concave bottom and differences in tolerances supplied by different manufacturers were common. Consequently, statistically different dissolution rates could be obtained when determined using containers obtained from two different manufacturers (12). Flask shape had affected the hydrodynamics of systems and consequently it was considered better to have flasks of uniform hemispherical shape. The flat-bottomed flask described in the BP 1980 (13) alleviated the problems of manufacturing tolerances in vessel shape. Irrespective of apparatus design, there are still several potential problems. The wire basket corrodes following exposure to acidic media; the basket method gives poor reproducibility due to inhomogeneity of the agitation conditions produced by the rotating basket; and clogging of the basket can occur due to adhering substances. Additionally, particles can fall from the rotating basket and sink to the bottom of the flask where they will not be subjected to the same agitation as that inside the basket.

## Paddle Apparatus

An apparatus described by Levy and Hayes (14) may be considered the forerunner of the beaker method. It consisted of a 400 ml beaker and a three-blade, centrally placed polyethylene stirrer (5 cm diameter) rotated at 59 rpm in 250 ml of dissolution fluid (0.1 *N* HCl). The tablet was placed down the side of the beaker and samples were removed periodically.

In the pharmacopoeial apparatus 2—the paddle apparatus method— a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should position no more than 2 mm at any point from the vertical axis of the vessel and rotate without significant wobble. The specifications of the shaft are given in Fig. 4. A distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating to prevent corrosion. Again typical arrangements for the apparatus are shown in Fig. 3. The dosage form is allowed to sink to the bottom of the flask before rotation of the blade commences. Sinkers are recommended to prevent floating of capsules and other floatable forms. A small, loose piece of nonreactive material (e.g., a few turns of wire helix) may be attached to the dosage form. Soltero et al. (15) thoroughly examined the influence of sinker shapes on dissolution rates obtained from gelatin capsules. Although a stainless steel helix is officially recommended, alternative shapes can greatly affect the dissolution rates.

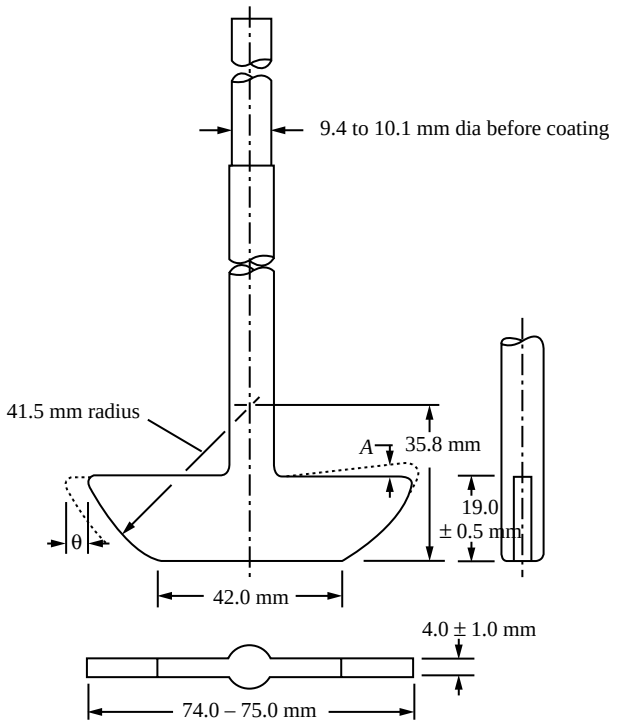


**Fig. 4** The paddle-stirring element of the United States Pharmacopeia 24. (From Ref. 8.)

## Data Presentation and Interpretation

The data collected during dissolution tests will, especially at the developmental stage, be presented as dissolution profiles (Fig. 5) whereby the amount released is plotted as a function of time. It is common practice to monitor drug release at several points or where possible continuously until 100% of the dose is dissolved and dissolution profiles showing drug release against time can be produced. Values equivalent to the times for 10, 50, 70, or 90% drug release are often cited ($t_{10\%}$, $t_{50\%}$, $t_{70\%}$, or $t_{90\%}$). The dissolution profiles from tablets and capsules are often sigmoidal in shape.

Pharmacopoeias generally do not require a dissolution profile to be determined but do specify that a certain amount of drug must dissolve within a specified time. Should a single time specification be stated, the test may be concluded in a shorter time if the requirement for a minimum amount dissolved is met. If two or more times are specified, then the samples should be withdrawn with a tolerance of $\pm 2\%$ of the stated time. For Digoxin Tablets B.P. (9), when there is more than one tablet per test, all six replicate runs should release at least 75% of the stated amount within 60 min.

The USP 24 (8) assesses dissolution in three stages. Should the specifications be met at either of the initial two stages, there is no requirement to proceed to later stages. In stage 1, six units are tested. To pass the test, each unit, at the specified time, should have $Q + 5\%$ in solution where $Q$ is the amount of dissolved active ingredient expressed as a percentage of the labelled content and 5% is the percentage of labelled content. Failure at stage 1 requires a second stage test on an additional six units. To pass the test at this stage, the average content dissolved, from the combined two stages, should be equal to or greater than $Q$ with no unit being less than $Q - 15\%$. Failure leads to stage 3 where a further 12 units are tested. These results are combined with the results from the previous stages. The average of the total of the 24 units thus tested should be equal to or greater than $Q$. No more than two units should be less than $Q - 15\%$ and no unit should be less than $Q - 25\%$.

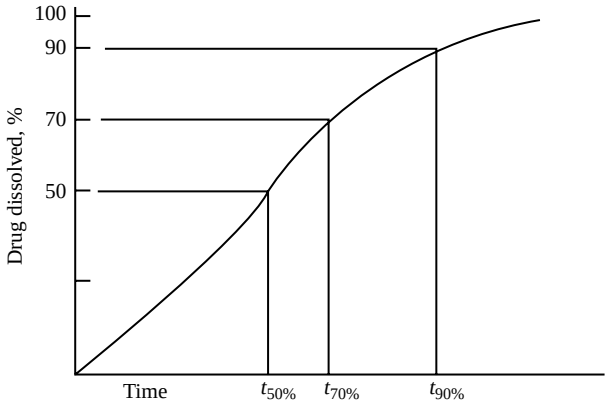


**Fig. 5** Dissolution profiles of a hypothetical dosage form indicating the determination of $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ values.

## Sample Collection Procedures

The USP 24 (8) and the BP 2000 (9) state that samples should be drawn from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. A volume of media equal to the volume of sample withdrawn should be replaced or compensated for by calculation. Samples removed should be filtered. Any substance released from the filter should contribute no significant absorption to the active ingredient in solution or interfere with the assay. No extractable materials interfering with the analytical procedures should be released. The filter pore size should not be greater than 1 μm. When capsule shells interfere with the analysis, the contents of a minimum of six capsules should be removed as completely as possible and the shells dissolved in the dissolution medium. This allows calculation of correction factors, which should be no greater than 25% of the labelled content.

## Factors That May Influence Dissolution

Both the BP 2000 (9) and the USP 24 (8) give considerable guidance about external factors that may influence dissolution. This section highlights some of the more important factors.

### Vibrations

No part of the assembly, including the environment in which the assembly is placed, should contribute significant motion, agitation, or vibration beyond that caused by a smoothly rotating element. There is little doubt that excessive vibration of the dissolution apparatus considerably increases dissolution rates. Therefore, to minimize the effects of vibration, the distance from the dissolution motor to the stand supporting it and the distance from the rotating basket to the point connecting the shaft to the dissolution motor should be specified (16). Vibrations may arise from various sources, including water bath and pump.

### Shaft

Many problems associated with variations in the dissolution rate are caused by misalignment. Limits should be set on shaft eccentricity. Minor changes in physical alignment of the paddle may produce large variations in results.

### Vessel

The use of a hemispherical flask allows some variation in construction. Minor changes in vessel shape may considerably alter the dissolution rates determined by the paddle method (17). Glass vessels with an inside bottom flatter than specified gave a high bias in dissolution rates and those with an inside bottom of steeper curvature gave a low bias. Such bias is associated with the different hydrodynamics created by the different shapes. Plastic vessels provide more perfect hemispheres than glass vessels and their shape is more reliable and should be preferred to glass containers provided the drug does not sorb to them and that the dissolution fluid does not interact with the plastic (17). However, plastic containers are not without their problems. During dissolution, some tablets may become more centred in glass vessels than in plastic vessels, which is probably attributable to friction between the tablet and the wetted vessel surface being greater for plastic than for glass (18).

### Sampling procedures

Flow through facilities usually allow ultraviolet (UV) analysis of drug dissolved or collection of samples for subsequent analysis (Fig. 3). Filtering must be accomplished before analysis to prevent insoluble excipients or dissolving drug particles from passing through the beam. Filters remove solid particles prior to assay at the stage of sample removal, reduce turbidity problems caused by undissolved drug and excipients, and help eliminate spurious results caused by particles dissolving following removal.

A sampling probe used for continuous sampling must not disturb the hydrodynamics of the system. When continuous monitoring is accomplished by flow-through systems, the flow rate should not be too high or some of the suspended drug will adhere to the filter, resulting in a percolation effect and artificially high estimates of the amount of drug released. Care should be taken with automatic flow methods so that tube length is kept to a minimum to reduce the amount of fluid in the tubing. Excessive amounts will produce long lag periods before dissolved material is transported from the dissolution vessel to the analyzing cell.

Adsorption of the drug onto the filter should be avoided and the release of isooctylphenoxypolyethoxyethanol, which is often included in the membrane filters as a wetting agent, may be a potential problem (19). This surfactant has significant absorption in the 220–240 nm wavelengths. Selection of a suitable pore size is important. Adsorption onto filters of frusemide was increased by using filters of decreasing pore size but of the same diameter (20). Replacement of sampled fluid must be by fluid of the same temperature as that inside the dissolution vessels. Recent developments have focused on the possibility of utilizing a UV-fiber-optic probe to pipe light in the dissolution medium where a spectrophotometric assay in situ through fiber-optic light guides may be carried out (21).

### Temperature control

The USP directs that the thermometer should be removed before the test and that the temperature should be checked periodically. The dissolution fluids should be maintained at 37 $\pm$ 0.5°C. Even slight temperature variations may have a significant effect on tablet dissolution.

### Deaeration of dissolution medium

The levels of dissolved gas are not specified in either the BP 2000 (9) or the USP 24 (8); each states that media should be deaerated before use. By testing the dissolution of prednisone tablets in water that had been presaturated with air, Cox et al. (22) showed that the media must remain unsaturated during the test. Higher initial air content resulted in increased percentages of drug dissolved during the paddle method. Air bubbles, in the media that contained higher levels of air, attached to particles of the disintegrating tablets owing to sorption of air. The particles did not sink to a mound at the bottom of the vessel but were suspended by the air bubbles and were, therefore, subject to greater conditions of agitation.

Failure to deaerate media used with the basket apparatus results in the clogging of the pores of the basket by air, causing different flow characteristics (19) and often a decrease in dissolution rates. This has even greater influence when gel-forming extended-release dosage forms are being tested. Bubbles attached to tablets or capsules may cause the dosage form to relocate near to the top of the basket, thereby reducing dissolution rates or amounts dissolved (19). The basket is intended to hold the tablet in a fixed position. Disintegration of the dosage form will occur in the basket and fluid must flow through the basket sufficiently to disperse the tablets and sweep dissolved drug into the bulk of the dissolution fluid.

### Variation in speed of agitation

Agitation speed must be uniform throughout the test. Some motor drives result in a satisfactory mean speed but during the test will periodically slow down or speed up. Consequently, speed should be checked at the start and end of each run (19).

## Standardization and Calibration

All apparatuses must be calibrated and the variables standardized and known. Experimental design in dissolution testing to examine residual variation between experimental runs and individual dissolution vessels is feasible (23). The objective is to minimize errors in experimental setup, achieved by using mean dissolution times and partial balancing. Lower coefficients of variation occur at higher hydrodynamic intensities. Dissolution tests are critical but difficult to carry out properly. Standardization should remove all variable factors. Similar problems of fluid flow exist with the current USP 24 apparatus, although the hemispherical shape will create different fluid hydrodynamics.

The USP 24 (8) specifies apparatus suitability tests, based on the operating conditions, involving the USP dissolution calibrator, disintegrating type or the USP dissolution calibrator, nondisintegrating type. The apparatus is deemed suitable if the obtained results are within the accepted range stated for that type of calibrator. Calibrators are used to show deficiencies in the equipment, for example, chain looseness, tilting of stirrer motor, excessive vibration, or misalignment of the flasks with the stirrers. Nondisintegrating calibrants are composed of 300 mg salicylic acid, whereas disintegrating calibrants contain 50 mg prednisone. The dissolution rates obtained from the calibrants should fall within established ranges at both 50 and 100 rpm.

## Other Variables in Compendial Methods

The BP 2000 (9) generally specifies 1000 mL of dissolution fluid, although for digoxin tablets the volume is 600 mL water. Dissolution fluid volume is varied more in the USP 24 (8). Examples include 500 mL (alprazolam tablets), 750 mL (metyrosine capsules), and 900 mL (ampicillin capsules). The volume may additionally vary as to the strength of the preparation. Thus, for phentermine hydrochloride capsules 500 mL of medium is used if the strength is 15 mg or less, but 900 mL is used for preparations containing in excess of 15 mg. Similar volumes are used for prednisone tablets where the cut-off point is 10 mg and for cinoxacin capsules where 500 mL is used for capsules containing 250 mg or less but 1000 mL is used for capsules containing in excess of 250 mg.

# OTHER METHODS USING LIMITED VOLUMES OF DISSOLUTION FLUIDS

Many other, nonofficial methods that use limited volumes of dissolution fluids have been described. These include the rotating-disc method that measures the dissolution rate from a constant surface area, which is usually in the form of a disc (24). Intrinsic dissolution rates, which relate dissolution rate to the surface area of the dissolving drug, can easily be determined from constant-surface area discs whose areas can be very easily estimated. The rotating filter-stationary basket apparatus (25) uses a large capacity (1.5 L) glass flask containing a stationary sample basket and a rotating-filter basket.

Other apparatuses that have been evaluated for dissolution testing include the magnetic basket apparatus (26) and the commercial Bio-Dis apparatus (27). In the later apparatus, the use of vertically reciprocating tubes, sealed with mesh discs at each end to restrain the dosage form was developed. The USP 24 (8) describes, as drug release apparatus 3, the reciprocating cylinder method. The tubes are raised up and down, 9.9–10.1 cm, in dissolution fluid. The apparatus has been advocated to monitor release from pellet systems although it tended to higher values of amount released than other apparatus (27).

Limited-volume apparatus, with a finite volume of dissolution fluid, suffer from the problem that they operate under non-sink conditions, which results in limitations when poorly soluble drugs are considered. Some apparatus, previously described, may be modified by the use of flow-through systems and reservoirs to provide sink conditions by removing solvent and replacing it with fresh solvent. Continuous circulation may also be used for conditions when sink conditions are not required. The drawbacks of nonflow-through apparatus (28) include (1) lack of flexibility, (2) lack of homogeneity, (3) the establishment of concentration gradients, (4) their semiquantitative agitation, (5) the obscuring of details of the dissolution processes, and (6) their variable shear. Consequently, flow-through apparatus characterized by a dissolution cell of low volume (often less than 30 mL) and a reservoir to provide fresh solvent have been developed.

## Flow-Through Apparatus

The USP 24 flow-through cell (24) may be either used in closed mode when the fluid is recirculated and, by

necessity, is of fixed limited volume, or open mode when there is continuous replenishment of the fluids. The basic components are reservoir, pump, heat exchanger, column, tablet support, filter system, and analytical method. The systems enable solvent to be taken from a suitable reservoir and passed straight through the apparatus containing the dosage form to be either assayed and removed (effluent system) or recirculated (recycling system) (Fig. 6).

The design of the pump to remove the solvent from the reservoir is crucial to the results obtained from such systems. The pump used may be either a displacement (oscillating or peristaltic) or a momentum (centrifugal) type. However, peristaltic pumps may create oscillations that result in faster dissolution rates than might otherwise have occurred. Dissolution is affected by factors such as the volumetric flow rate, the cross-sectional area of the cell, the initial drug quantity, liquid velocity, and drug concentration.

Ascending fluid flow is used. Flow-through facilities remove some of the problems associated with non-sink conditions. The material under test (tablet, capsules, or granules) is placed in the vertically mounted dissolution cell, which permits fresh solvent to be pumped (between 240 and 960 mL/h) in from the bottom. Glass beads (1 mm diameter) control the flow across the whole cross-sectional area of the cell. Cells may have diameters of 12 or 22.6 mm.

The maintenance of a controlled flow is crucial to column methods and can be influenced by the inlet system. The design of the apparatus was improved by using a holder constructed of a folded wire cross above the inlet pipe to support the tablet such that the solid is bathed in the outflow contained within a concentric column of relatively stationary liquid (29). It is common to place the tablets on such supports, but attrition (by glass beads) may encourage breakdown of the dosage form thereby increasing dissolution rates. Tablet support and consistent positioning in the liquid flow are prerequisites for consistent results. Attempts have been made to embed the tablet in glass beads.

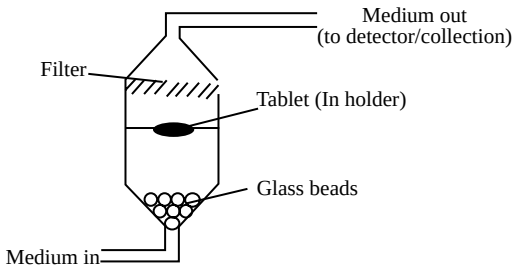


**Fig. 6** Schematic diagram of a flow-through dissolution cell.

## DISSOLUTION MEDIA

Ideally, a dissolution medium should be formulated as close as possible to that pH anticipated in in vivo fluids; for example, dissolution media based on 0.1 *N* HCl are used to mimic gastric pH. Simulated gastric fluid is similarly used. Food can increase the gastric pH to as high as 3–5. Many compendial dissolution fluids are at a pH near neutral despite the fact that tablets, when swallowed, will meet a lower gastric pH. The use of surfactants and enzymes may also be a coarse approximation of the intestinal fluids, although surfactants may be included to increase drug solubility by solubilization into micelles. Both the USP 24 (9) and the BP 2000 (8) indicate that the pH of dissolution-fluid should be within 0.05 of that specified in the relevant monograph.

The inclusion of alcoholic solvents, for example, isopropanol, has been advocated for insoluble drugs such a norethindrone and was used to provide a rank order of dissolution (30). The dissolution rates increased in hydro-alcoholic medium. Each component of a norethindrone–mestranol combination tablet gave its own dissolution rate in deaerated water but was not discriminated in the hydro-alcoholic medium. Therefore, for quality control purposes, all components of a multiple drug formulation should have their dissolution assessed. Problems are induced by the inclusion of cosolvents. Alcoholic solvents may retard dissolution rates by retarding disintegration as, for example, during the dissolution of chlorthalidone into 40% aqueous methanol (31).

Sink conditions may be accomplished by using dissolution media consisting of two phases to allow partition of the drug into the organic phase; the use of organic solvents such as hexane may provide sink conditions. Supramicellar surfactant concentrations may be used for drugs of low solubility (<0.01% w/v). Consequently, sodium dodecyl sulfate may be added to the media. However, the inclusion of surface agents into the dissolution media may make the media less discriminatory. The use of 0.4% sodium dodecyl sulfate was proposed as an alternative to 0.1 or 0.01 *M* HCl for the dissolution of rifampin (32) because the drug was more stable in surfactant solutions. After 1 and 2 h, in 0.01 *M* HCl, 13 and 29% of rifampicin decomposed, at 37°C. After 2 h, only 2% degraded in water.

## IN VITRO–IN VIVO CONSIDERATIONS

Ideally, dissolution tests should provide data to distinguish good and bad formulations, changes in production processes that might influence bioavailability, batch to batch reproducibility, site and manufacturer variation, and information on the stability of the product. The test is used in the development of new dosage formulations, for quality control and to give indications for bioequivalence. In addition, one may consider the dissolution testing as a prognostic tool for in vivo performance (33).

Great care must be taken to produce good in vitro–in vivo correlations. This may be accomplished by creating a reproducible dissolution method that provides proper selection of medium, degree of agitation, etc. Ideally, this could be achieved if the gastrointestinal tract conditions were successfully reconstructed in the dissolution apparatus.

Using dissolution parameters, dissolution rate can be related to bioavailability for some drugs. For example, Kingsford et al. (34) showed a linear relationship between the percentage dissolved in 30 min and the bioavailability of frusemide relative to an oral solution when frusemide was examined using the rotating basket apparatus and buffer at pH 5.0. Therefore, in certain cases, it may be appropriate to apply dissolution testing data to evaluate biopharmaceutical implications of a product change rather than automatic bioequivalence study (35). The USP 24 (8) details the requirements for in vitro and in vivo evaluation of dosage forms, including immediate release and modified release dosage forms.

## DISSOLUTION TESTING OF MODIFIED-RELEASE ARTICLES

The USP 24 (8) also gives tests (termed "drug-release" tests rather than dissolution tests) for modified release products, which includes extended-release (sustained or slow-release) products and delayed-release (enteric-coated) articles. The former are described as allowing at least a two-fold reduction in the dosing frequency as compared with that drug presented as a conventional dosage form. A delayed-release article is one that releases the drug at a time other than promptly after administration.

The USP 24 testing of both extended-release articles and delayed-release articles proceeds via three stages. For extended-release products three time points are generally specified, expressed in terms of the labelled dosing interval ($D$ in hours). The amounts dissolved ($Q$) at each time interval are expressed in terms of the labelled content; the limits embrace each value of $Q$, the amount dissolved at each specified dosage interval (8). Initially six units are tested. No unit should lie outside the stated range or be less than the stated amount at the final test time. Failure at this stage leads to examination of a further six units whose results are combined with the initial results. The average of the 12 units should not lie outside the stated range and should not be less than the stated amount at the final test time. Additionally none should be more than 10% outside each of the stated ranges and none more than 10% of the labelled content below the stated amount at the final test time. Failure to meet these standards requires the testing of a further 12 units, the data being combined with those from the previous 12 units. The average of the 24 units is within each of the stated ranges and not less than the stated amount at the final test time. No more than two of the 24 units should release more than 10% outside each of the stated ranges; no more than two of the 24 units should release more than 10% below the stated amount at the final test time; and none of the units should be more than 20% of the labelled content outside each of the stated ranges or more than 20% of the labelled content below the stated amount at the final test time.

## DISSOLUTION TESTING FOR ENTERIC-COATED TABLETS AND CAPSULES

The USP 24 (8) describes two general methods for delayed-release (enteric coated) articles, each method utilizing a change in pH. In method A, an acid stage consisting of 750 mL of 0.1 *M* HCl is used. An aliquot is withdrawn after 2 h for assay. The pH is then raised by adding 250 mL of 0.2 *M* tribasic sodium phosphate and adjusted to pH 6.8 $\pm$ 0.05 and the dosage forms are operated for a further 45 min. Method B utilizes 1000 mL of 0.1 *M* HCl operated for the initial 2 h period and the fluid is completely replaced with 1000 mL pH 6.8 phosphate buffer and run for 45 min. Again, three levels of testing are used for the HCl stage (8).

In addition to the official tolerances for delayed-release products, commercial manufacturers will have their own in-house specifications. Standards for enteric-coated forms ensure the integrity of the coat, but consideration should be given to a pH change method for evaluating extended-release medications. This evaluation should ensure that

dose dumping does not occur at a specific pH, as might be a problem with delayed-release dosage forms based on, for example, hydroxypropyl methylcellulose phthalate.

## DRUG RELEASE FROM SUSTAINED-RELEASE ARTICLES

There have been various testing schedules that have been developed to study the influence of pH changes, for example, from 0.1 *N* HCl to pH 7.5 (36) or a progressive rise from pH 1.5, 4.5, 6.9, 7.2–7.5 over 22 h (37). Such changes are designed to follow the pH changes during the passage of a dosage form through the gastrointestinal tract, but the residence time in the tract can be as little as 4–6 h up to in excess of 24 h depending on the food that the patient has ingested. An alternative approach is to develop topographic profiles of the matrix tablets to determine the dissolution profiles at a variety of pHs (38); an apparent three-dimensional profile of amount released versus time versus pH is produced. Such profiles may be used to determine over which pH range dosage forms release their drug at a faster rate than required, thus avoiding the problem of dose dumping at a particular narrow pH range.

In the development stage of new modified release dosage forms, it is vitally important to not only consider dissolution testing as a quality control tool but also as a prognostic tool to discriminate in vivo good and bad formulations. Therefore, one needs to understand the mechanism of drug release from the dosage form in order to utilise the dissolution testing effectively. For extended-release reservoir formulations, where the drug was dissolved and released by diffusion through a barrier coat, factors such as the influence of medium on solubility of the drug need to be established.

In the case of hydrophilic-matrix sustained-release formulations, drug release is via diffusion through and erosion of the hydrated viscous surface polymer. Therefore, factors that may provide additional strength or support to this surface polymer, must be minimised. For example, during the dissolution testing of a large swelling matrix, it may be supported by the basket wall, which combined with slow speed of rotation leads to unrealistically slow drug release. This is in contrast to in vivo where due to agitation of the GIT and also presence of food, the level of erosion is greater and thus faster drug release may occur. A discriminating dissolution testing would assist the formulator to achieve the desired in vivo drug release profiles, through the formulation variables.

Figure 7 illustrates how the type of apparatus and also speed of rotation influences the in vitro drug release profiles of a HPMC matrix formulation (39). In another study, using HPMC matrix formulations, the in vitro data were successfully correlated to in vivo data with an excellent correlation when apparatus 1 at 150 rpm was used (40).

Matrix-sustained release tablets may present additional problems since they tend to stick to the side walls of the vessel, giving a reduction in the partial exposure of surface area and the use of the paddle may destroy the discreteness of the dosage form. Moreover, media containing high concentrations of phosphates may result in the disintegration of sustained-released matrices based on hydroxypropyl methycellulose.

Pellets, beads, and other particulate systems intended to provide prolonged release are probably best tested by column methods that facilitate changes in pH or dissolution fluids. With compendial apparatuses, problems arise; for instance, it is difficult to capture dispersed particles when the paddle method is used, and small particles may pass through the mesh of the basket in the basket method.

Recently a simple (41) model was proposed using mathematical indices to define a similarity factor $f_2$, to compare dissolution profiles as in Equation (4):

$$f_2 = 50 \log\{[1 + 1n_t^{n=1}(R_t - T_t)^2]^{-0.5} \times 100\} \quad (4)$$

where $R_t$ and $T_t$ are percent dissolved at each time point for the reference product and the test product, respectively. Using the $f_2$ values, dissolution profiles are considered dissimilar if these values were less than 50 with average difference between any dissolution samples not being greater than 50%. The similarity factor and a similarity

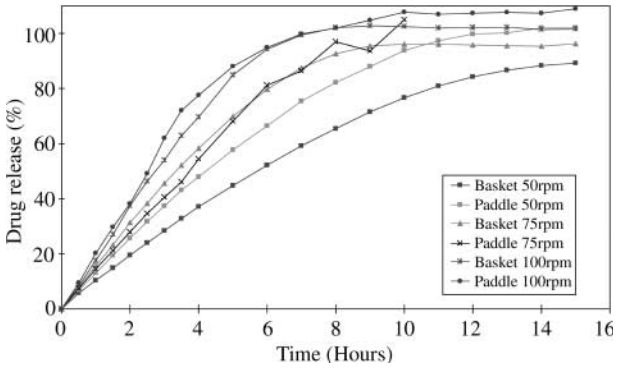


**Fig. 7** Dissolution profiles of diltiazem hydrochloride from a swelling matrix system in phosphate buffer pH 6.8 at 37°C, using the basket and paddle methods rotating at 50, 75, and 100 rpm.

testing have been recommended for dissolution profile comparison in the FDA Guidance for Industry (35, 42, 43).

## SUPPOSITORIES AND OTHER SEMISOLIDS

Semisolids are intended for percutaneous (ointments, creams, gels, patches), vaginal (pessaries), ophthalmic (ointments, creams, gels), or rectal (ointments, creams, suppositories, gels) release. Some estimate of drug release is desirable to ensure that the drug is not entrapped by preferential partitioning into the oleaginous phase. Unlike tablets and capsules, there must be some constraint on the surface area of such preparations exposed to dissolution fluids to produce a quantitative estimate of release during dissolution studies.

Suppositories create problems because they soften, deform, disintegrate, and change from a solid to an oily state during the test. Glass beads will control the interfacial area during a dissolution test; consequently, the use of a continuous-flow bead-bed column-type apparatus was advocated for the dissolution of suppositories (44). Suppositories based on soluble carriers such as polyethylene glycol create fewer problems in the assessment of drug release since the carrier rapidly dissolves. However, oleaginous-based suppositories (e.g., containing cocoa butter) will melt slowly and spread, giving a constantly changing surface area. Consequently, membranes are frequently employed to entrap the suppository although they may themselves be the factor that limits drug transport. In addition, basket methods are unsuitable since the basket mesh will readily clog although polyurethane baskets of dimension similar to the USP basket have been used. To design a realistic apparatus for both types of suppository probably require two phases.

Transdermal patches have also been examined. The USP 24 (8) includes reference to transdermal drug delivery systems. The temperature of operation is specified as 32 ± 0.5°C. Apparatuses include a modified paddle method, using a disc, 41.2 mm in diameter, to locate the patch at the bottom of the dissolution flask, a cylinder method whereby the patch is attached to the outside of a stainless steel cylinder of radius approximately 2.2 cm and rotated in the dissolution flask, or a reciprocating disc apparatus such that the disc may be reciprocated at 30 cycles/min over an amplitude of 2 cm in volumetrically calibrated solution containers.

## ROBOTICS

Dissolution by manual methods is very labor-intensive and time-consuming. Therefore, the use of microprocessors is cost-justified, especially when some tests may take up to 24 h. Robotics speed up assay techniques; rapid insertion and withdrawal of a small sample probe, controlled robotically, produces minimum disturbance of the hydrodynamic conditions. The use of robotics increases the speed of assay, the throughput and the productivity of dissolution testing. However, the speed of assay may then be the rate-limiting step to productivity. Consequently, to speed up the assay process, short high-pressure liquid chromatography (HPLC) columns may be used to increase assay speed.

## ASSAY METHODS

Whatever assay technique is chosen, it must be specific to the drug under assay. For single-drug entities, UV or HPLC assays are most suitable and most used; even ion-specific electrodes can be used to monitor drug release in the presence of a suitable anion or cation. However, with any trend to multiple dosage forms, more complicated assay techniques may be required, which makes HPLC useful since more than one drug can be analyzed in the same chromatogram. The use of UV photodiode array spectrophotometry has become popular with multidrug dosage forms.

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